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EXAMINER

WHITEMAN, BRIAN A

ART UNIT

PAPER NUMBER

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/600,358	ROIFMAN, CHAIM M.
	Examiner Brian Whiteman	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on _____.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-39 is/are pending in the application.

4a) Of the above claim(s) 6,8,16,18,23-26,28,29 and 34-39 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-5,7,9-15,17,19-22,27 and 30-33 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 25 September 2000 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 18.

4) Interview Summary (PTO-413) Paper No(s). _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: 7.

DETAILED ACTION

Non-Final Rejection

Claims 1-3, 4(b), 5(b,c,d,e), 7, 9-14, 15(b), 17, 19-22, 27, 30(b), 31, 32, 33(a,b) are pending examination.

Applicant elects Group II, claims 1-22, 27, 30(b), 31, 32, and 33(a,b) relating to the Lyp protein of SEQ ID NO: 4 with traverse in paper no. 13. Applicant traverses the restriction because no lack of unity was raised during the national phase; Rather than relying on PCT rules, the examiner appears to have considered the US rules for unity of invention and does not appear to have taken into account the fact that the international examiner did not raise any such unity objection; SEQ ID NO: 2 and SEQ ID NO: 4 fall within the scope of broad claim 1; international authorities did not appear to find it overly burdensome to conduct a search for the subject matter claimed herein. See pages 1-2.

Applicant's traversal is acknowledged and is not found persuasive for the following reasons: the inventions listed as Groups I-XIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT rule 13.2, they lack the same or corresponding special features for the following reasons:

37 CFR 1.475(c) states:

"If an application contains claims to more or less than one of the combination of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present."

37 CFR 1.475(d) also states:

"If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and 1.476(c)."

37 CFR 1.475(e) further states:

"The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternative within a single claim."

In view of 37 CFR 1.475 (c), 37 CFR 1.475 (d), and 37 CFR 1.475 (e). Group I is considered the main invention to the product first mentioned in the claims (claim 1), and the first recited invention drawn to other categories related thereto, e.g. a method of making (claim 27), method of use (claim 30b).

The inventions listed as Groups I-XIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the reasons set forth in paper no. 10.

As the technical feature linking the members of the listed in claim does not constitute a special feature as defined by PCT Rule 13.2, particularly since the compound(s) and/or substance(s) listed in the claims do not share a structural feature in common with respect to their site of action. Thus, the requirement of unity of the invention is not fulfilled.

As set forth above and in paper no. 10; the examiner followed the guidelines under PCT Rule 13.1 and 13.2 provided by the MPEP and under the guidelines the restriction is deemed proper. In addition, other than asserting that the international examiner did not consider a lack of

Art Unit: 1635

unity and that it would not be an undue burden in the examiner to search the subject matter claimed herein, the applicant has not provided sufficient guidance to overcome the lack of unity. Thus, the examiner followed the PCT lack of unity guidelines provided by the MPEP and in view of the numerous groups it would be an undue burden on the examiner to search the entire subject matter herein.

The restriction is deemed proper and is made **Final**.

Claims 1 and 13 link(s) inventions I and II. The restriction requirement between the linked inventions is subject to the non-allowance of the linking claim(s), claims 1 and 13. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or non-statutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable.

In re Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claims 4a, 5a, 6, 8, 15a, 16, 18, 23-26, 28-29, 30a, 33c, and 34-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Information Disclosure Statement

The international search report for PCT/CA99/00038 has been considered.

Priority

Acknowledged is made to Canadian application 2,220,853 filed on 1/16/98 and that this application is 371 of PCT/CA99/00038 filed on 1/18/99.

Drawings

NOTE: In the next response, please submit a response (proposed corrections or corrections to the PTO 498) because a PTO 498 is filed with this non-final rejection. If the reply to the rejection does not have a response to the PTO 498, the response will be considered non-responsive. See 37 CFR 1.121(d) and 1.85(a).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

Claims 4, 5, 15, 30, and 33 are objected to because of the following informalities: In view of the election/restriction these claims read on non-elected embodiment. Appropriate correction is required.

Claims 7, 9, 17, and 19 are objected to because of the following informalities: the corresponding SEQ ID NO: for each sequence in Table 4 should be added as in claim 4.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 5(c,e), 7, 9, 11-12, 27, 33(a) as best understood, are readable on a genus of an isolated polynucleotide comprising a polynucleotide sequence encoding a Lyp protein and/or an isolated polynucleotide which encodes a Lyp protein having an amino acid sequence greater than 70%, 80%, 90% overall identity to the amino acid sequence of SEQ ID NO: 4, wherein the genus of an isolated polynucleotides disclosed herein is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-14, 17, 19, 21-22, and 33(b), as best understood, are readable on a genus of a Lyp protein and/or a protein with 70%, 80%, 90% overall identity to the amino acid sequence of SEQ ID NO: 4 and/or a peptide comprising at least one functional domain of a Lyp protein or at least one antigenic determinant of a Lyp protein, wherein the genus of a Lyp protein and/or a protein with a desired overall identity to the amino acid sequence of SEQ ID NO: 4 are not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 30(b), as best understood, are readable on a genus of a transgenic non-human animal comprising an insertion of a polynucleotide encoding a heterologous Lyp gene, wherein the genus of the transgenic animals are not claimed so that they could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of isolated DNA encoding a Lyp polypeptide and/or an amino acid sequence with at least a desired overall identity to SEQ ID NO: 4. The as-filed specification provides sufficient description of a species of an isolated DNA coding a human polypeptide in SEQ ID NO: 4 (specification names it Lyp2) or the DNA sequence of SEQ ID NO: 3 which encodes an isoform of intracellular tyrosine phosphotase (Lyp

1). The disclosure states that, "Lyp is pre-dominantly expressed in lymphoid cell lineages and Lyp 1 is 808 amino acids long and Lyp2 is only 692 amino acids long." Furthermore, the specification states that the last 123 amino acids of Lyp 1 are absent from Lyp 2 and are replaced by unique residues and this is highly suggestive of major differences in the regulation of the activity of the two isoforms." In addition, the specification states that, "the significance of the alternative C-terminal of Lyp1 and Lyp2 remains unclear." Therefore, in view of the lack of guidance for what amino acids and/or nucleotides are considered essential for a genus of a nucleotide sequence encoding a Lyp protein and/or a Lyp protein and/or at least one functional domain and/or at least one antigenic determinant of a Lyp protein, the as-filed specification does not provide sufficient description of a genus of nucleotide sequence and/or sequences that shares at least 70%, 80%, 90% overall identity to SEQ ID NO: 4.

Furthermore, the specification contemplates a genus of transgenic animals comprising a nucleotide sequence encoding a heterologous Lyp gene. The starting material for making a transgenic animal is a nucleotide sequence encoding a Lyp gene. The specification provides sufficient description of SEQ ID NO: 3 or the peptide of SEQ ID NO: 4, however, the specification does not provide sufficient description of any transgenic animal comprising a sequence encoding a Lyp gene and its corresponding phenotype. Therefore, in view of the lack of sufficient description of the corresponding phenotype, one skilled in the art could not envision the phenotype of any transgenic animal comprising a sequence encoding a Lyp protein.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are

essential for the genus of any nucleotide sequence encoding a Lyp protein and/or Lyp protein and/or sequences with greater than 70%, 80%, or 90% overall identity to SEQ ID NO: 4 and/or a non-human animal comprising a polynucleotide encoding a Lyp gene; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a Lyp protein and/or amino acid sequences with greater than 70%, 80%, or 90% overall identity to SEQ ID NO: 4 and/or at least one functional domain of a Lyp protein and/or at least one antigenic determinant of a Lyp protein that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of isolated DNA encoding a Lyp polypeptide and/or a polynucleotide which encodes a Lyp protein with greater than 70% overall identity to the amino acid sequence of SEQ ID NO: 4 and/or amino acids sequences greater than 70% overall identity to amino acid sequence set forth in SEQ ID NO: 4 and/or at least one functional domain of a Lyp protein and/or at least antigenic determinant of a Lyp protein and/or a transgenic non-human animal comprising a polynucleotide encoding a Lyp gene, if the claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming an unspecified genus of an amino acid sequences and/or nucleotide sequences and/or transgenic non-human animals that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v.*

Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed DNA sequences encoding a Lyp protein and/or amino acid sequences encoding a Lyp protein and/or non-human transgenic animals that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-3, 4(b), 5(b, c, e), 7, 9, 10-14, 15(b), 17, 19-22, 27, 30(b), 31-32, and 33(a,b) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) An isolated polynucleotide comprising a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 4; 2) A recombinant vector comprising the polynucleotide of 1; 3) A host cell comprising the recombinant vector of 2; 4) A peptide comprising the amino acid sequence set forth in SEQ ID NO: 4; 5) A method for producing the polypeptide of SEQ ID NO: 3; comprising culturing the host cell of 3 under conditions in which the polypeptide is expressed and isolating the polypeptide therefrom; 6) An isolated polynucleotide wherein the nucleotide sequence consist of the nucleotide sequence set forth in SEQ ID NO: 3; and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of DNA sequences encoding a Lyp protein and/or a Lyp protein and/or amino acid sequence with a desired percent of overall identity to the amino acid sequence of SEQ ID NO: 3 and/or a transgenic non-human animal comprising a polynucleotide encoding a Lyp protein, respectively, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended.

With respect to the claimed invention, which encompasses a Lyp protein, the specification fails to provide sufficient guidance and/or factual evidence for what are the functional and structural limitations of a Lyp protein. The specification provides two novel polynucleotide sequences (Lyp1 and Lyp2) that have a tyrosine phosphotase and share the first 685 amino acids (page 11). However, the final 123 amino acids of Lyp1 are absent in Lyp2 and replaced with several unique residues, which makes the biological activity of Lyp2 distinct from Lyp1 (page 11). Therefore, in view of the breadth of the term "Lyp protein" and the inconsistency of what constitutes a Lyp protein because the sequences are novel and the functions are distinct from one another, it would take one skilled in the art an undue amount of experimentation to make and/or use any Lyp protein in view of the lack of guidance for the definition of what constitutes a Lyp protein.

Furthermore, with respect to the claimed invention, the specification contemplates using nucleotide sequences, which hybridizes under stringent conditions to the nucleotide sequence encoding SEQ ID NO: 3. In view of the state of the art and the lack of guidance provided by the as-filed specification for what conditions are considered stringent, it is not apparent to one skilled in the art if any of nucleic acid sequence, which hybridizes under any condition would possess the same biological activity compared to SEQ ID NO: 3 (Lyp2) discovered in a human. Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 23-228), it would required undue experimentation for one skilled in the art to arrive at other peptides that have Lyp activity. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other peptides that have Lyp or Lyp2 activity, it certainty would require undue experimentation to make their corresponding DNA and, therefore any other nucleotide sequence is not enabled by the specification other than the nucleotides sequence set forth in SEQ ID NO: 3 or the amino acid sequence of SEQ ID NO: 4.

Furthermore, with respect to claims encompassing using a nucleic acid sequence with at least 10, 15, 20 consecutive nucleotides of SEQ ID NO: 3 and/or peptide comprising at least 5, 10, or 20 consecutive amino acids of SEQ ID NO: 4, one skilled in the art would reasonably determine from the specification and the art of record that the fragments are contemplated for use as primers or as a probe which hybridizes specifically to the nucleotide sequence SEQ ID NO: 3 or 4, the as-filed specification contemplates fragments that hybridize preferentially to SEQ ID NO: 3 or SEQ ID NO: 4, but not to any other nucleic acid sequence. However, the state of the prior art as exemplified by Wallace et al. (Methods Enzymol, Vol. 152, pp. 432-443, 1987) and Sambrook et al. (Molecular Cloning, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 11.47) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, the as-filed specification does not provide sufficient guidance to determine the structural and functional limitation of a nucleic acid probe which hybridizes specifically to the DNA of SEQ ID NO: 3 or polypeptide of SEQ ID NO: 4 of the claimed invention under any stringent condition wherein said stringent hybridization condition prevents said nucleic acid probe from hybridizing to DNA other than SEQ ID NO: 3 or 4. The lack of working examples in view of the prior art and the as-filed specification would result in an undue amount of experimentation for one skilled in the art to reasonably correlate to any DNA probe that would meet the functional and structural limitations of the claimed embodiment. There are no suggestions as to what the target sites in SEQ ID NO: 3 or 4 are or what modifications can be made while retaining the functional limitation. In addition, claims 10 and 20 are the only claims to a limitation of the nucleic acid (*e.g.* that is at least 10, 15, or 20 nucleotide bases long; probe

of claim 10 that **comprises** at least ten consecutive bases from SEQ ID NO: 3 or a peptide comprising at least 5, 10, 20 consecutive amino acids of SEQ ID NO: 4). Since the nucleotide sequence mentioned merely **comprises** at least five peptides of SEQ ID NO: 4 or ten consecutive nucleotides from a nucleotide sequence from SEQ ID NO: 3, it encompasses any random sequence of any length as long as it has a stretch of at least 5 peptides that is the same as SEQ ID NO: 4 or at least ten contiguous nucleotides that is the same as SEQ ID NO: 3. Furthermore, since there is no limitation that the claimed nucleic acid be complementary to the nucleotide sequence at the stretch of at least five peptides of SEQ ID NO: 4 or ten contiguous nucleotides that is the same as SEQ ID NO: 4, the structural limitations encompass any nucleotide sequence consisting of at least 5 peptides or at least 10 consecutive nucleotides. Thus, claims 10 and 20 encompass any nucleic acid consisting of at least 5 peptides or 10 nucleotides in length and hybridizes to DNA of SEQ ID NO: 4 or 3, respectively. Since the structural limitations of the claims clearly cover any nucleic acid that is at least 5 consecutive peptides or 10 consecutive nucleotides in length and in view of the unpredictable nature of the art and lack of guidance with respect to appropriate modifications, one skilled in the art would have to make and test with further experimentation an enormous number of nucleic acids that meet the structural limitations to determine which probes also meet the functional limitation. This amount of experimentation would result in undue experimentation for one skilled in the art. Therefore, based on the unpredictable nature of the invention and the state of the prior art, the limited guidance and working examples in the as-filed specification, and the extensive quantity of experimentation needed to identify the nucleic acids encompassed by the claims, it would require an undue amount of experimentation to identify or make the nucleic acids encompassed by the claims.

Furthermore with respect to claims 30-32, the specification discusses that the invention features a genus of transgenic non-human animal, with the insertion of a polynucleotide encoding a heterologous Lyp gene and goes on to contemplate that there are techniques for producing the transgenic animals (page 22-24). The specification provides prior art pertaining to methods for generating transgenic animals using pro-nuclei injection (pages 23-24). In addition, the as-filed specification provides the second method for producing transgenic mice, which involves modification of embryonic stem cells using transgenic DNA (page 23).

The specification requires that the starting material, which is a nucleic acid encoding a Lyp polypeptide, be used in a method of making a transgenic non-human mammal comprising a polynucleotide encoding a heterologous Lyp gene. The phenotype of the transgenic animal is not provided by the as-filed specification because there are no working examples encompassing the production of a transgenic non-human animal.

It is further to note that the as-filed specification contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic animals for used in the claimed invention. See pages 22-24 of the as-filed specification. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's

health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission is unpredictable. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only “putative” ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, “The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far.” Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic mammal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal other than mice, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic mammals comprising a polynucleotide encoding a heterologous Lyp gene. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate

from the specification and the prior art to any method of producing transgenic animal comprising an insertion of a polynucleotide encoding a heterologous Lyp gene. However, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence encoding the Lyp polypeptide is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human animal.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic mammal comprising a transgenic sequence encoding a heterologous Lyp gene, which expresses the transgenic sequence such that a phenotype occurs. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any transgenic mammal of the invention. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic mammal expressing a polynucleotide encoding a heterologous Lyp gene.

[Note that although the claimed transgenic mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic mammal having cells, which harbor a recombinant

nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. Lyp protein) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human animals as claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic animal. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animal comprising a transgene of interest (e.g. Lyp); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. Lyp) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification

does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic animal using microinjection of transgene into germ line and producing a transgenic animal which comprises a transgenic sequence encoding Lyp gene and which expresses the protein in the transgenic animal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that “a given construct may react very differently from one species to another.” See page S39, Summary. Wall et al. report “transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies.” See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic animal that expresses Lyp, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic animal comprising a transgenic sequence encoding a Lyp polypeptide and which over-expresses the protein in the transgenic animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1-6, listed above. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the lack of guidance for using amino acid sequences as primers does not reasonably extrapolate to the full scope of the claimed invention encompassing the use of primers for amplifying any unknown DNA molecule encoding a mutated polypeptide of SEQ ID NO: 3 or amino acid sequence set forth in SEQ ID NO: 4. Furthermore, the disclosure does not provide sufficient guidance in view of Chiu et al., *Folding and Design*, 1998, pp. 23-228 and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Furthermore, the working examples for the demonstration or the reasonable correlation to the production of any transgenic animal, in particular when the expression of the Lyp must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human animals of any species, and the breadth of the claims drawn to any transgenic non-human animal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-4, 5(e), 7, 9-14, 15(b), 19-22, 27, 30(b), and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "Lyp protein" in claims 1-4, 5(e), 7, 9-15, 21-22, 27, 30(b), 31-33 is a relative term, which renders the claim indefinite. The term "Lyp protein" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term because the claimed fail to particularly point out and distinctly claim what is a Lyp protein. Furthermore, the two proteins (Lyp1 and Lyp2) listed in the claimed invention possess different functional properties (Lyp1 is expression is increased in active lymphoid cells and Lyp2 is not expressed in active lymphoid cells (page 11).

The phrase "hybridizes under stringent conditions" in claim 5(e) is a relative phrase, which renders the claim indefinite. The phrase "hybridizes under stringent conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The definition of the phrase "hybridizes under stringent conditions" is not a closed definition from reading page in the as-filed specification. The parameters of what constitutes moderately or highly stringent conditions are not defined by the claims.

The phrase "with at least 80% overall identity, preferably at least 90% overall identity" in claims 7 and 19 is a relative phrase, which renders the claims indefinite. The phrase "with at least 80% overall identity, preferably at least 90% overall identity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The

disclosure does not define the metes and bonds of the phrase and it is not apparent what percent each claim is particularly pointing out and distinctly claiming.

The phrase "sequence comprising at least 10, preferably 15 and more preferably 20 consecutive nucleotides" in claim 10 is a relative phrase, which renders the claim indefinite. The phrase "sequence comprising at least 10, preferably 15 and more preferably 20 consecutive nucleotides" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bonds of the phrase and it is not apparent what percent the claim is particularly pointing out and distinctly claiming.

The phrase "peptide comprising at least 5, preferably 10, more preferably 20 consecutive amino acids" in claim 20 is a relative phrase, which renders the claim indefinite. The phrase "sequence comprising at least 10, preferably 15 and more preferably 20 consecutive nucleotides" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bonds of the phrase and it is not apparent what percent the claim is particularly pointing out and distinctly claiming.

The statement in claim 11, "**a** polynucleotide of claim 1" is indefinite because it does not point out which polynucleotide **a polynucleotide** is referring to in the claim. The dependent claim should state "...**the** polynucleotide of claim 1". The independent claim encompasses a single isolated polynucleotide and the independent claim encompasses several isolated polynucleotides.

The statement in claim 5(e), “**a** nucleotide sequence of (b)” is indefinite because it does not point out which nucleotide sequence **a nucleotide** is referring to in the claim. The dependent claim should state “....**the** nucleotide of (b)”.

Claim Rejections - 35 USC § 102

In view of the indefiniteness of the term “Lyp protein” under 112 second, and to the extent that any nucleic acid sequence other than the non-elected invention that comprises a tyrosine phosphatase domain and is expressed in the lymphoid, the following 102 rejections apply.

Furthermore, with respect to the hybridization conditions in claim 5e, any nucleotide sequence that binds to the SEQ ID NO: 3 reads on the claimed invention because the parameters for what constitutes stringent conditions is not defined by the claims.

In addition, with respect to claims 10 and 20, any nucleotide sequence comprising 5, 10, or 20 consecutive amino acids of SEQ ID NO: 4 or 10, 15, 20 consecutive nucleotides of SEQ ID NO: 3 reads on the claimed invention because of the indefiniteness and the breadth of the claims.

Furthermore, because of the phrase “complementary to said nucleotide sequence of SEQ ID NO: 3” in claim 5, any sequence with one base pair that is complementary to a base pair from the sequence will read on the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5c, e, 7, 9, 10, 11, 12, 13, 17, 19-22, 27, and 33(a,b) are rejected under 35 U.S.C. 102(b) as being anticipated by Matthews et al. (IDS, Mol. Cell. Biol., Vol. 12, pp. 2396-2405, 1992). Matthew teaches a nucleotide sequence (has a tyrosine phosphotase domain and is expressed in the lymph node) with 84.5% identity to amino acid of SEQ ID NO: 4. Matthew further teaches the isolation and sequence analysis of cDNA clones and PTPase domain of PEP was also isolated and cloned by PCR and clones into bacterial expression system (page 2397). In addition, Matthew teaches a nucleotide sequence with at least 20 consecutive nucleotides with the nucleic acid sequence encoding SEQ ID NO: 4.

Claims 1-3, 5c, e, 7, 9-14, 17, 19-22, 27, and 33(a,b) are rejected under 35 U.S.C. 102(a) as being anticipated by Lasky et al. (IDS, WO 97/35019). Lasky teaches a nucleotide sequence (protein tyrosine phosphotase) with 99.7% identity to amino acid SEQ ID NO: 4. Lasky further teaches vectors containing and capable of expressing the nucleic acid (abstract).

Claims 1-3, 5c, e, 10, 11-14, 21-22, 27, and 33(a,b) are rejected under 35 U.S.C. 102(a) as being anticipated by Bahija et al. (US Patent No. 6228641). Bahija teaches a nucleotide sequence (with a tyrosine phosphotase domain and is expressed in human thymus and overexpressed in lymphomas) with 88.1% identity to SEQ ID NO: 3 (DNA). Bahija further teaches vectors containing and capable of expressing the nucleic acid (abstract).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

Brian Whiteman
Patent Examiner, Group 1635
5/31/02


DAVE T. NGUYEN
PRIMARY EXAMINER